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STATE-OF-THE-ART REVIEW

Protective effects of neutrophil serine protease inhibition against ischemia–reperfusion injury in lung or heart transplantation

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Transplanted organs are inevitably exposed to ischemia–reperfusion (IR) injury, which is known to cause graft dysfunction. Functional and structural changes that follow IR tissue injury are mediated by neutrophils through the production of oxygen-derived free radicals, as well as from degranulation which entails the release of proteases and other pro-inflammatory mediators. Neutrophil serine proteases (NSPs) are believed to be the principal triggers of post-ischemic reperfusion damage. Extended preservation times for the transplanted donor organ correlate with heightened occurrences of vascular damage and graft dysfunction. Preservation with α1-antitrypsin, an endogenous inhibitor of NSPs, improves primary graft function after lung or heart transplantation. Furthermore, pre-operative pharmacological targeting of NSP activation in the recipient using chemical inhibitors suppresses neutrophilic inflammation in transplanted organs. Hence, effective control of NSPs in the graft and recipient is a promising strategy to prevent IR injury. In this review, we describe the pathological functions of NSPs in IR injury and discuss their pharmacological inhibition to prevent primary graft dysfunction in lung or heart transplantation.

Introduction

Ischemia–reperfusion (IR) injury, an unavoidable pathological phenomenon that occurs during organ transplantation, is defined as the paradoxical changes in both structure and function that take place following the re-establishment of blood flow after an episode of ischemia in a given tissue [1] (Box 1). Multiple

Abbreviations
AAT, α1-antitrypsin; AATD, α1-antitrypsin deficiency; BALF, bronchoalveolar lavage fluid; BOS, bronchiolitis obliterans syndrome; CatC, cathepsin C; COPD, chronic obstructive pulmonary disease; DPP1, dipeptidyl peptidase 1; HTx, heart transplantation; IR, ischemia–reperfusion; LTx, lung transplantation; LVADs, left ventricular assist devices; NCFB, noncystic fibrosis bronchiectasis; NE, neutrophil elastase; NSPs, neutrophil serine proteases; PAH, pulmonary arterial hypertension; PR3, proteinase 3.

Box 1. Medical term definitions commonly used in the field of organ transplantation.

- *Ischemia* is a condition in which blood flow (and thus oxygen) is restricted or reduced in a part of the body.
- *Cold ischemia* is defined as the period of graft storage *ex vivo* under hypothermic conditions.
- *Reperfusion* is the restoration of blood flow to an organ or tissue after it has been blocked.
- *Ischemia-reperfusion injury*, also known as reoxygenation injury, is the tissue damage caused when blood supply returns to tissue (reperfusion) after a period of ischemia or lack of oxygen (anoxia or hypoxia).
- *Primary graft dysfunction* is a syndrome of acute lung injury that occurs within the first 72 h after lung transplantation.
- *Orthotopic lung transplantation* is a surgical procedure where a healthy lung from a donor is transplanted into its normal anatomical position within the recipient's body.
- *Heterotopic heart transplantation* is a surgical procedure in which a heart is transplanted into a location within the recipient's body that differs from its normal anatomical position.

pathological processes contribute to IR injury, including cell damage, oxidative stress, intracellular calcium overload, energy metabolism disorder, endoplasmic reticulum stress, extracellular matrix remodeling, as well as the release by activated neutrophils of inflammatory cytokines and neutrophil serine proteases (NSPs) [2–6]. NSPs, activated by cathepsin C (CatC) during early neutrophil differentiation in the bone marrow, are degradative enzymes that trigger post-ischemic reperfusion injury.

Lung transplantation (LTx) is the treatment of choice for numerous patients suffering from end-stage pulmonary disease. Each year, more than 4600 lung transplantations (LTx) are carried out globally, with 55% in North America and 36% in Europe [7]. LTx remains the best option for improving the quality of life in patients afflicted with chronic inflammatory lung diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), noncystic fibrosis bronchiectasis (NCFB), α1-antitrypsin deficiency (AATD), pulmonary arterial hypertension (PAH), and interstitial lung disease. A significant challenge associated with this thoracic surgical procedure is primary graft dysfunction, which represents the major cause of early post-transplantation morbidity and mortality [8]. This dysfunction is caused by IR injury during reperfusion of the ischemic lung transplant.

Heart failure affects a global population exceeding 64 million individuals, with approximately 5% of heart failure patients reaching the end-stage [9,10]. Heart transplantation (HTx) is recognized as the optimal treatment method for selected patients with end-stage heart failure [11]. Despite its effectiveness, primary limitations include the scarcity of available heart grafts and the adverse effects of long-term immunosuppressive therapy. Striking a balance between preventing rejection and minimizing the associated risks linked to prolonged immunosuppression (such as susceptibility to infections, malignancies, and nonimmune toxicities like diabetes, hypertension, and renal insufficiency) deserves careful consideration [12]. Additionally, the occurrence of IR injury during HTx is inevitable and closely linked to post-operative complications, including graft dysfunction and diminished graft survival [13,14]. These findings underscore the necessity for strategies aimed at minimizing the impact of IR injury in transplantation.

In this review, we present an overview of NSPs, their physiopathological properties, and their pharmacological inhibition in LTx or HTx. Our focus is on graft preservation with α1-antitrypsin (AAT), the major endogenous inhibitor of NSPs, and premedication of the recipient with a CatC inhibitor before transplantation.

Neutrophil serine proteases

Neutrophils play a critical role in the innate immune response to infection and in the regulation of inflammatory processes. A key component of the neutrophilic activity is the secretion of the proteolytically active NSPs, neutrophil elastase (NE), proteinase 3 (PR3), cathepsin G (CatG), and NSP-4. While the physiological function of NSP-4 remains to be determined, other NSPs are known to play a role in inflammation-related tissue damage and to thusly complicate tissue repair following injury [15]. NSPs are initially produced as inactive glycosylated precursors, or 'zymogens' [15,16], to avoid unwanted intracellular protein proteolysis in the promyelocyte stage of neutrophil differentiation within the bone marrow. They are primarily activated through the action of the ubiquitous cysteine dipeptidyl aminopeptidase, CatC (also referred to as dipeptidyl peptidase 1 (DPP1)) [17,18], which removes the N-terminal 2-residue propeptides of NSP zymogens (Fig. 1). A recent study provided further evidence to support the existence of an alternative, non-CatC-dependent activation of NSPs in

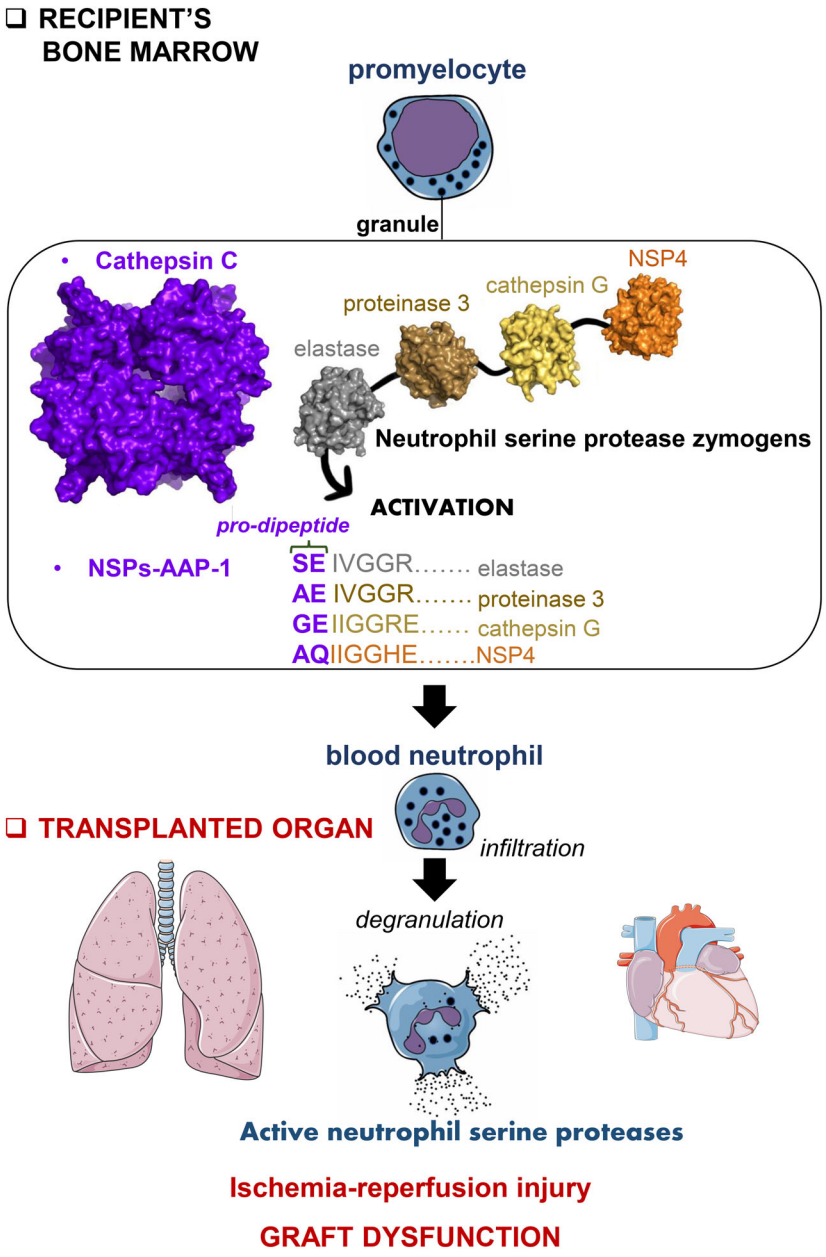

Fig. 1. Effect of neutrophil serine protease activities on ischemia–reperfusion injury in organ transplantation. Neutrophil serine proteases (NSPs) are initially produced as inactive 'zymogens' during the promyelocyte stage of neutrophil differentiation within the recipient's bone marrow. They are primarily activated through the action of cathepsin C (CatC), which removes the N-terminal 2-residue propeptides of NSP zymogens. A CatC-independent activation pathway involving a cysteine protease termed NSPs-AAP-1 (NSPs-alternative activating protease-1) is involved in the activation of < 10% of NSPs [19]. Following lung or heart transplantation, an excessive release of active NSPs without adequate counterbalance and regulation by endogenous protease inhibitors contributes to ischemia–reperfusion injury induced graft dysfunction.

humans and mice, that involves a cysteine protease called NSPs-AAP-1 (NSPs-alternative activating protease-1) [19]. Under physiological conditions, mature NSPs fulfill crucial functions in both intracellular and extracellular bacteria elimination and in modulating inflammatory processes [20,21].

Physiologically, NSP-mediated proteolytic activity is controlled by endogenous inhibitors. AAT, belonging to the serpin superfamily, is one such NSP inhibitor that is primarily synthesized in the liver by hepatocytes and secreted into the bloodstream during an acute-phase response. Under inflammatory or infectious conditions, its serum concentrations can surge up to four times within a matter of hours [22]. AAT's function is to protect tissues from damage caused by NSPs [15,23,24]. AAT is currently used clinically to treat emphysema caused by AAT deficiency [25], a genetically inherited condition in which impaired AAT production increases the risk for lung or liver disease. The lung symptoms of AAT deficiency typically resemble those of emphysema and include cough with sputum production, shortness of breath, and wheezing. Signs of liver involvement in AAT deficiency may include swelling of the legs or abdomen,

jaundice, vomiting of blood, or blood in the stools. Likewise, there exists evidence of NSP involvement in chronic inflammatory diseases, auto-immune disorders, and cancer [15,16,26], that is, when excessive release of active NSPs is not adequately counterbalanced by endogenous inhibitors [15]. NSPs also actively contribute to IR injury in organ transplantation by processing extracellular matrix components such as elastin, fibronectin, proteoglycan, and collagen [27].

To re-establish a balance between NSPs and their endogenous inhibitors, CatC inhibitors have been developed. The prolonged administration of the reversible CatC inhibitors, $IcatC_{XPZ-01}$ [28,29], brensocatib [30], BI-9740 [31], BI-1291583 [32], and HSK31858 [33] has been shown to result in sufficient inhibitor levels in the bone marrow to counteract CatC and significantly reduce downstream NSP activation, thereby achieving anti-inflammatory, protective effects in animal models. *In vivo* findings suggest the advantage of pharmacological CatC targeting, opening avenues for potential drug repurposing strategies. Brensocatib [34], BI-1291583 [35], and HSK31858 are being evaluated in clinical trials in patients with chronic inflammatory lung diseases (Table 1, Fig. 2). Positive topline results from Phase 3 ASPEN study of brensocatib in patients with bronchiectasis were recently announced. The results validate CatC inhibition as new mechanism of action with potential to address a range of neutrophil-mediated diseases.

Table 1. Reversible chemical cathepsin C inhibitors under clinical trials.

Brensocatib	Phase 3	Noncystic fibrosis bronchiectasis (pending approval)	NCT04594369
	Phase 2	Chronic rhinosinusitis without nasal polyps (CRSsNP)	NCT06013241
BI-1291583	Phase 2	Noncystic fibrosis bronchiectasis	NCT05846230
	Phase 1	Cystic fibrosis bronchiectasis	NCT05865886
HSK31858	Phase 2	Noncystic fibrosis bronchiectasis	NCT05601778

Protective effects of neutrophil serine proteases inhibition against primary graft dysfunction following lung transplantation

Preservation of lung graft with α1-antitrypsin

Preserving organ viability outside of a living organism can be achieved through methods such as storage at either warm or cold temperatures, with or without perfusion. The risk of vascular damage and primary graft dysfunction rises as the preservation times for transplanted donor lungs extend. The shortage of available donor lungs and the risk of IR injury also limit LTx. As a result, the preservation of donated lungs in

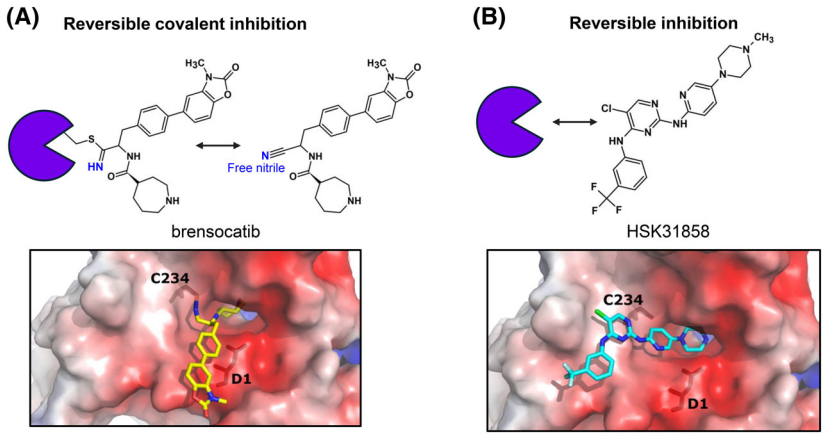

Fig. 2. Model structures of brensocatib (A) or HSK31858 (B) in complex with CatC. (Top) Brensocatib is a reversible and covalent inhibitor of cathepsin C (CatC). Formation of a reversible thioimidate complex resulting in the reaction of the nitrile function with the active site cysteine 234 is shown. HSK is a reversible noncovalent inhibitor of CatC. (Bottom) Solvent-accessible surfaces of CatC complexed with inhibitors. Electrostatic surface potentials are colored red and blue for negative and positive charges, respectively, and gray color represents neutral residues. The carbon atoms of the inhibitors are shown in green. The oxygen, nitrogen, chlorine, and fluor atoms are colored in red, blue, dark green, and light turquoise, respectively. The electrostatic surface was calculated using APBS, the adaptive Poisson–Boltzmann solver [51], as implemented in the PYMOL (Delano Scientific, San Carlos, CA, USA) plugin. The continuum electrostatics calculations used for the surface draw were calculated by using the PDB2PQR software [52]. Calculations were performed at pH 7.0. Structures were generated using the program PYMOL.

protein-free, dextran-containing electrolyte solutions (e.g., Perfadex) is typically restricted to approximately 6 h. The use of normo- or hypothermic *ex vivo* perfusion of lung allografts might significantly extend the acceptable preservation time, but valid clinical data are still missing, and the logistical and financial burden is very high. To develop a novel lung preservation protocol suitable for clinical application in lung transplant patients, Götzfried *et al.* [36] evaluated the protective effects of AAT-containing Perfadex on NSP-mediated proteolytic damage. The authors employed a mouse orthotopic LTx model, preserving the transplant in Perfadex containing AAT (1 mg·mL^{-1}) for an extended cold ischemia period of 18 h. The objective of this preclinical investigation was to examine if adding AAT in the perfusion solution during cold ischemia could prevent vascular leakage and immediate neutrophil-mediated inflammation after reperfusion. Additionally, the authors determined whether the anticipated improvement of graft function can be attributed to the direct antiprotease activity of AAT. Remarkably, the addition of AAT to Perfadex led to a nearly 40% increase in blood oxygenation within the transplanted left lung. AAT-treated lungs exhibited significantly lower protein and neutrophil levels in the bronchoalveolar lavage fluid (BALF), along with reduced neutrophil infiltration in the transplanted lung following 4 h of reperfusion. Thus, the addition of AAT into Perfadex reduces primary graft dysfunction and early neutrophil responses after prolonged storage for 18 h at 4 °C, followed by 4 h of reperfusion in the recipients. In agreement with the study results, recipients lacking both NE and PR3 activities in neutrophils also experience protection from early reperfusion injury [36]. Conversely, lung allografts perfused with an AAT mutant lacking inhibitory activity, do not exhibit the same protective effects [36]. This work strongly supports then notion that NSPs, the principal targets of AAT, play a significant role as major triggers of post-ischemic reperfusion damage in LTx [36].

Premedication of recipients with a cathepsin C inhibitor before lung transplantation

Rehm *et al.* [37] evaluated the potential beneficial effect of preventing NSP activation in the bone marrow through CatC inhibition. In a mouse orthotopic LTx model, recipient animals were treated with Icat$C_{XPZ\text{-}01}$ for 10 days, prior to LTx. Left lung allografts were perfused with Perfadex and kept in Perfadex at 4 °C for 18 h, constituting a period of cold ischemia and recipient mice underwent orthotopic transplantation of the left lung; analyses were performed 4 h after reperfusion. Recipient mice that received Icat$C_{XPZ\text{-}01}$ displayed a disappearance of active NSP proteins in the transplanted lung and a reduction in NSP activities in bone marrow neutrophils. The administration of Icat$C_{XPZ\text{-}01}$ also resulted in a significant increase in the partial oxygen pressure (pO_2) of the left ventricle blood compared to the group treated with the vehicle. Thus, prolonged administration of Icat$C_{XPZ\text{-}01}$ before surgery enhanced the quality and function of the transplanted lung immediately after surgery (Table 2). Furthermore, this study presented supporting data for the protective effect of Icat$C_{XPZ\text{-}01}$ on post-operative lung function, noting a significant decrease in the immediate inflammatory response following reperfusion. The BALF analysis revealed a significant decrease in neutrophil content in Icat$C_{XPZ\text{-}01}$-treated recipient compared to lungs from vehicle-treated mice, indicating the preservation of the capillary barrier following Icat$C_{XPZ\text{-}01}$ treatment [37] (Table 2). This work also showed that NSPs play a significant role as major triggers of post-ischemic reperfusion damage in LTx.

Protective effects of neutrophil serine proteases inhibition against graft dysfunction following heart transplantation

Preservation of heart grafts with α1-antitrypsin

Currently, cold static storage still represents the standard technique for preserving donor hearts before transplantation, although the use of *ex vivo* allograft machine perfusion is rapidly increasing, especially in North America [38]. However, novel preservation strategies are required to attenuate graft dysfunction caused by IR injury and subsequently improve clinical outcomes. In our experimental model of heterotopic HTx, we have demonstrated that adding human AAT to the preservation solution Custodiol enhances the functional recovery of grafts after cardioplegic arrest, *ex vivo* prolonged hypothermic storage, and *in vivo* blood reperfusion [39]. Our data showed that neutrophil infiltration into the myocardial tissues, as evidenced by myeloperoxidase-positive cells, was decreased by AAT in grafts subjected to prolonged cold ischemia. Furthermore, our computational analysis shows that heart grafts from the AAT network display higher homogeneity, more positive gene correlations, and fewer negative gene correlations than the grafts from the placebo network [39]. Additionally, in an experimental pancreatic islet transplantation model, AAT has been observed to reduce inflammation and improve survival [40].

Table 2. Beneficial clinical outcomes in graft functions following transplantation in recipient animals treated with a cathepsin C inhibitor. HTx, heart transplantation; LTx, lung transplantation; NSPs, neutrophil serine proteases.

Lung transplantation	
Preclinical model	Mouse orthotopic LTx model
	8–10-week-old male C57BL/6J mice
Premedication	$IcatC_{XPZ-01}$
Vehicle	15% (2-hydroxypropyl)-β-cyclodextrin dissolved in 50 mM citrate, pH 5
Pre-operative cathepsin C inhibitor treatment	Subcutaneous administration, 10 days, twice a day, 1.25 per kg body weight
Bone marrow inhibition of NSPs (%)	Elastase: ~ 75%, Proteinase 3: ~ 75%; Cathepsin G: ~ 75%
Graft	Left lung
Cold ischemia	18 h, 4 °C
Reperfusion	4 h, 37 °C
Donor lung function assessment	4 h after LTx
Beneficial clinical effects in graft functions	Reduction of neutrophils in BALF
	Preservation of the capillary barrier
	Improved gas exchange function
Heart transplantation	
Preclinical model	Rat heterotopic HTx model
	9–10-week-old male Lewis rat
Premedication	BI-9740
Vehicle	0.5 Natrosol 250 HX Pharm vehicle
Pre-operative cathepsin C inhibitor treatment	Oral administration, 12 days, 20 $mg \cdot kg^{-1}$ body weight
Bone marrow inhibition of NSPs (%)	Elastase: 42 ± 2%; Cathepsin G: 54 ± 4%
Graft	Heart
Cold ischemia	1 h, 4 °C
Reperfusion	1 h, 37 °C
Donor heart function assessment	1 h after HTx
Beneficial clinical effects in graft functions	Reduction of infiltrated neutrophils
	Reduction of irregularly arranged fiber and less edema
	Significant shortening in graft re-beating time after reperfusion
	Increased systolic function
	Increased rate pressure product
	Increased myocardial relaxation

Recently, Ding *et al.* [41] demonstrated that AAT alleviates endothelial dysfunction, prevents increased caspase-3, -8, -9, and -12 levels, and decreases apoptotic DNA breakage in vascular grafts obtained from brain-dead rats, which were subjected to IR injury.

Premedication of graft recipient with a cathepsin C inhibitor before heart transplantation

In a recent study, Liu *et al.* explored the effects of prolonged CatC inhibition using BI-9740 in a rat model of heterotopic HTx [31]. Their objective was to examine the influence of NSP activities on IR injury. The findings indicated that NSP proteolytic activities are markedly decreased in BI-9740-treated rats compared to those of the placebo group [31]. Accordingly, histological lesions observed in the hearts of the placebo-treated group are reduced in BI-9740-treated rats. Additionally, inhibition of NSPs diminishes neutrophil infiltration in the myocardium, alleviates nitro-oxidative stress, and decreases DNA damage after HTx in rats [31]. Consequently, this leads to an enhancement in the function of the left ventricular graft following heterotopic HTx [31]. This study provides experimental evidence that pharmacological inhibition of CatC improves graft function following HTx in rats.

Role and inhibition of other cathepsins in experimental models of transplantation

Cathepsins are proteases that are categorized into multiple families. These include serine proteases (cathepsins A and G), aspartyl proteases (cathepsins D and E), and the better-known cysteine proteases (cathepsins B, C, F, H, K, L, O, S, V, W, and Z). Several experimental transplantation models have investigated the effects of CatB and CatS. An *in vivo* orthotopic LTx mouse model was used to study the role of CatB in the pathophysiology of bronchiolitis obliterans syndrome (BOS) [42], a severe and progressive lung

disease characterized by inflammation and fibrosis of the bronchioles. BOS is often a complication following LTx leading to obstruction and irreversible lung damage. Preclinical results showed that CatB and collagens were upregulated 14 days post-transplantation. Furthermore, the study demonstrated that orthotopic transplantation in CatB knockout ($CatB^{-/-}$) mice significantly mitigated the histopathological and physiological features of graft rejection [42]. In allogenetically transplanted mice, CatS activity in the spleen was significantly increased 1 week after transplantation compared to syngeneic controls [43]. CatS, along with protease-activated receptor (PAR)-2, has been identified as a potential molecular target in acute renal allograft rejection [44]. Additionally, inhibition of CatS using a pharmacological inhibitor or genetic knockout of its target, PAR-2, alleviated chronic allograft vasculopathy in a murine heterotopic aortic transplantation model [45].

Clinical potential of cathepsin C pharmacological inactivation

Patients on LTx and HTx waiting lists usually suffer from severe end-stage pulmonary and heart diseases, respectively. Specialized, cost-intensive care and medical supervision are required for these patients. End-stage lung disease often deteriorates due to chronic inflammatory processes, as observed in conditions such as COPD, cystic fibrosis, NCFB, and AATD. Implantable left ventricular assist devices (LVADs) have benefited patients with advanced heart failure where other treatments have been ineffective or as a bridge to HTx. Additionally, patients with heart failure experience several changes in the electrical function of the heart that predispose them to potentially lethal cardiac arrhythmias. There is increasing evidence that associates inflammation with both atrial and ventricular arrhythmias. The conventional immunosuppression protocols employed in recipients of lung or heart transplants, chiefly consist of calcineurin inhibitors (cyclosporine, tacrolimus); an adjunct immunosuppressant (e.g., azathioprine, everolimus, or mycophenolate mofetil); and corticosteroids. These protocols have been shown to effectively decrease the risk of early graft loss attributed to acute rejection [46]. However, immunosuppressive strategies are also accompanied by undesirable side effects, not the least being an increased susceptibility to infection [47].

CatC inhibitors, currently under assessment in NCFB of CF patients, are well tolerated and deemed ethically acceptable for long-term application. CatC inhibition is also a potential therapeutic approach in other neutrophil-mediated inflammatory lung diseases such as COPD or AATD [15, 16, 34]. Importantly, such patients are susceptible to develop neutrophil-mediated end-stage pulmonary disease and to be added to a transplant waiting list. Pre-operative CatC inhibitor treatment is expected to suppress the inflammatory response initiated by the local release of NSPs from infiltrating neutrophils in the patient after LTx (Fig. 3). In an *in vivo* setting represented by a human model of heart failure, the presence of CatG and cathepsin L-like proteases (cathepsins B, K, L, S) was reported in cardiac biopsies from 22 patients before LVAD implantation (pre-LVAD), post-implantation (post-LVAD), and in patients with heart failure undergoing medical therapy. The authors suggested a parallel activation of molecules promoting the detrimental effect of extracellular matrix degradation, such as CatG and CatS. These modifications were associated with the inflammatory environment occurring after the LVAD implantation [48]. If patients with end-stage heart failure exhibit local release of NSPs and the presence of cysteine cathepsins, new targeted therapeutics could be identified, or drug repurposing could be considered. The heart of these patients could be protected while awaiting HTx, protected against IR injury during HTx, and protected from cardiac arrhythmias. Both the 24-week Phase 2 trial [49] and the 52-week Phase 3 trial (ClinicalTrials.gov Identifier: NCT04594369) with brensocatib in patients with NCFB support the use of CatC inhibitors in clinical practice. In this regard, it is important to note that the multiple redundant mechanisms of neutrophil antimicrobial responses are generally not impaired by CatC inhibitor treatment [16,50]. Treating high-risk patients, categorized as high priority on the transplant waiting list, could therefore benefit from this repurposing of available drugs.

Conclusions and perspectives

A major complication of organ transplantation is primary graft dysfunction, which represents the leading cause of early post-transplantation morbidity and mortality. Novel preservation and therapeutic strategies are therefore required to prolong graft survival. In this context, clear evidence implicating NSPs in IR injury and primary graft dysfunction following organ transplantation has been obtained in preclinical studies. Supplementation of classical preservation solutions or machine perfusion solutions with AAT and preoperative depletion of NSPs in circulating neutrophils by premedication with a CatC inhibitor in recipients

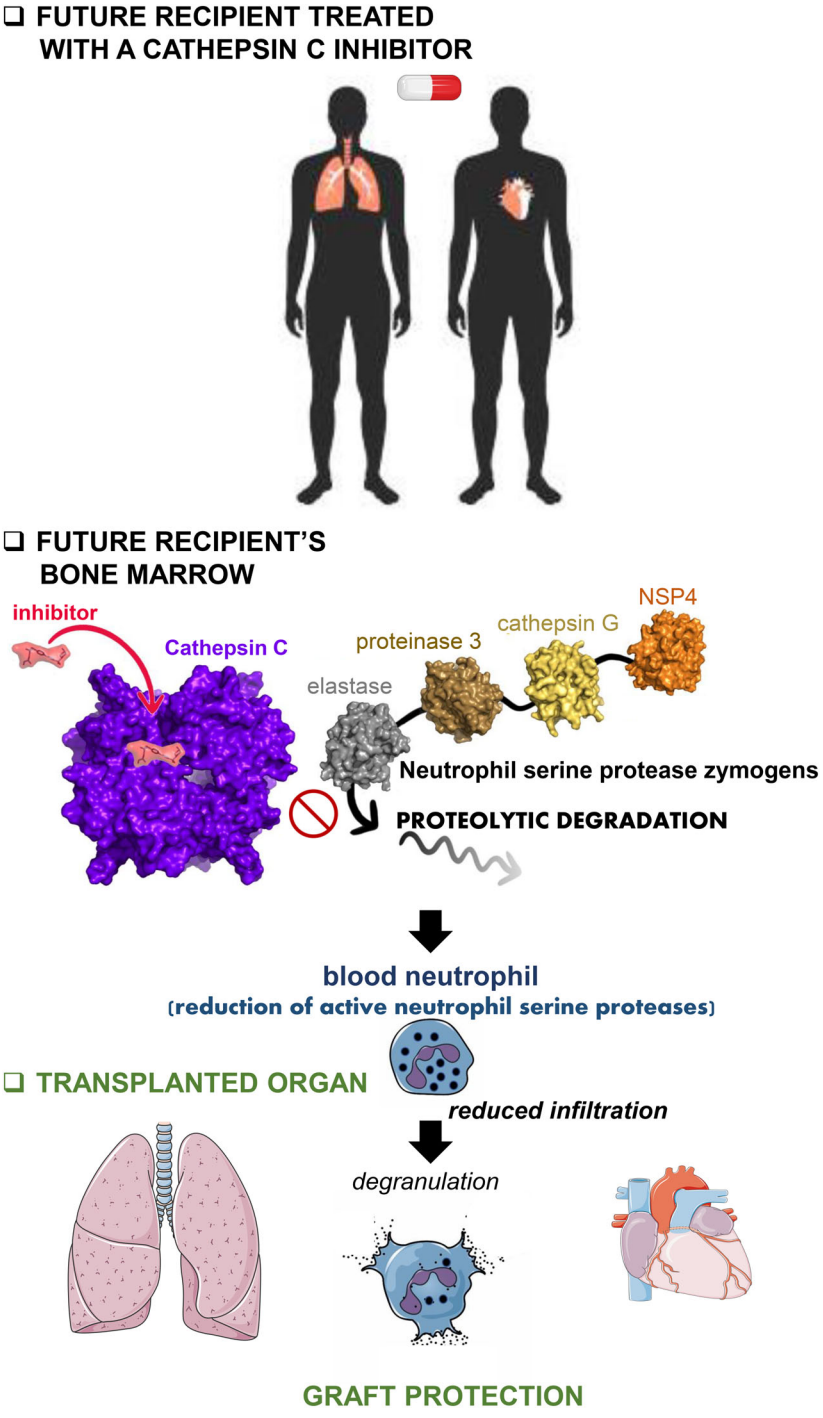

Fig. 3. Graft protection in premedicated recipients using a cathepsin C inhibitor. Cathepsin C (CatC) inhibition represents a potential therapeutic approach to treat recipients awaiting lung or heart transplantation. Pre-treatment with a CatC inhibitor, reaching sufficient levels in the bone marrow, inhibits CatC, and decreases downstream activation of neutrophil serine proteases (NSPs). Unstable NSP zymogens are proteolytically degraded during neutrophil differentiation in the bone marrow and circulating neutrophils display low amounts of active NSPs. Consequently, reduced blood neutrophils infiltration and better control of secreted NSPs alleviating ischemia–reperfusion-induced graft dysfunction are expected.

could prevent early post-operative complications and the development of primary graft dysfunction. It would be valuable to investigate the combination of both treatments: oral pretreatment of recipients with a CatC inhibitor prior to transplantation, followed by *in vitro* supplementation of the preservation solution with AAT during organ conservation in the ischemia period of the transplantation procedure. AAT is currently used clinically to treat emphysema caused by AAT deficiency and CatC inhibitors, currently undergoing evaluation in clinical trials, could be quickly translated into clinical practice for patients suffering from severe end-stage pulmonary or heart diseases and awaiting organ transplantation.

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Conflict of interest

Brice Korkmaz has been paid for the time spent as a committee member for advisory boards (Brensocatib Advisory Board (BRAB) INSMED, USA), as well as for other forms of consulting (Boehringer Ingelheim (Germany), Neuprozyme Therapeutics Aps (Denmark), Santhera Pharmaceuticals (Switzerland), Chiesi (Italy), Gerson Lehrman Group (GLG) (USA)), symposium organization (INSMED), and travel support, lectures or presentations, outside the submitted work. Patrick P. McDonald is also employed as Executive Director, Research at Insmed Inc. Insmed was however not involved in this work; did not fund it; and does not endorse it, implicitly or otherwise. Other authors declare no competing financial interests.

Author contributions

BK and SK-I wrote the manuscript. BK and AG prepared the figures. All authors participated in writing the manuscript by reviewing drafts and approving the final version.

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